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      (FILE 'HOME' ENTERED AT 15:05:28 ON 12 FEB 2003)

      FILE 'USPATFULL, PCTFULL, JAPIO' ENTERED AT 15:05:52 ON 12 FEB 2003
L1         96958 FILE USPATFULL
L2         28525 FILE PCTFULL
L3          8744 FILE JAPIO
      TOTAL FOR ALL FILES
L4        134227 S UREA OR (MONOACETYL(3A)UREA) OR (DODECYL (3A) UREA) OR (DIPHE
L5        101965 FILE USPATFULL
L6         29128 FILE PCTFULL
L7          2702 FILE JAPIO
      TOTAL FOR ALL FILES
L8        133795 S SODIUM CHLORIDE
L9          2163 FILE USPATFULL
L10          636 FILE PCTFULL
L11           78 FILE JAPIO
      TOTAL FOR ALL FILES
L12         2877 S ( MONO(1W)CARBOXYLIC(1W) ACID ) OR (CYCLIC(1W) CARBOXYLIC(1W)
L13        19583 FILE USPATFULL
L14         3498 FILE PCTFULL
L15         2064 FILE JAPIO
      TOTAL FOR ALL FILES
L16        25145 S ( MONOCARBOXYLIC ACID ) OR (CYCLICCARBOXYLIC ACID)
L17         1846 FILE USPATFULL
L18          558 FILE PCTFULL
L19           61 FILE JAPIO
      TOTAL FOR ALL FILES
L20         2465 S ( MONO-CARBOXYLIC ACID ) OR (CYCLIC-CARBOXYLIC ACID)
L21         1846 FILE USPATFULL
L22          558 FILE PCTFULL
L23           61 FILE JAPIO
      TOTAL FOR ALL FILES
L24         2465 S ( MONO CARBOXYLIC ACID ) OR (CYCLIC CARBOXYLIC ACID)
L25        20851 FILE USPATFULL
L26         3877 FILE PCTFULL
L27         2134 FILE JAPIO
      TOTAL FOR ALL FILES
L28        26862 S L12 OR L16 OR L24
L29        70706 FILE USPATFULL
L30        27871 FILE PCTFULL
L31         5837 FILE JAPIO
      TOTAL FOR ALL FILES
L32       104414 S LACTIC OR GLYCOLIC OR LACTATE OR (SODIUM (3A) (LACTATE OR LAC
L33       231523 FILE USPATFULL
L34        67838 FILE PCTFULL
L35        19197 FILE JAPIO
      TOTAL FOR ALL FILES
L36       318558 S L4 OR L8 OR L28 OR L32
L37       521097 FILE USPATFULL
L38       122461 FILE PCTFULL
L39       105728 FILE JAPIO
      TOTAL FOR ALL FILES
L40       749286 S PETROLATUM OR (PARAFFIN) OR (MICROCRYSTALLINE WAX) OR (MICROC
L41        30789 FILE USPATFULL
L42        19977 FILE PCTFULL
L43         1065 FILE JAPIO
      TOTAL FOR ALL FILES
L44        51831 S L36 (3S) L40
L45           14 FILE USPATFULL
L46           45 FILE PCTFULL
L47            0 FILE JAPIO
      TOTAL FOR ALL FILES
L48           59 S L44 AND ASCOMYCIN
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L49          3003 FILE USPATFULL
L50          9790 FILE PCTFULL
L51            55 FILE JAPIO
     TOTAL FOR ALL FILES
L52         12848 S L44 (5S) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN OR OINTMEN
L53           136 FILE USPATFULL
L54           690 FILE PCTFULL
L55             0 FILE JAPIO
     TOTAL FOR ALL FILES
L56           826 S L52 AND (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCOMYC
L57            31 FILE USPATFULL
L58           242 FILE PCTFULL
L59             0 FILE JAPIO
     TOTAL FOR ALL FILES
L60           273 S L52 AND ( FK-506 OR FR-900520 OR ASCOMYCIN )
L61             1 FILE USPATFULL
L62           103 FILE PCTFULL
L63             0 FILE JAPIO
     TOTAL FOR ALL FILES
L64           104 S L52 (3S) (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCOMY
L65         28450 FILE USPATFULL
L66          8904 FILE PCTFULL
L67          1044 FILE JAPIO
     TOTAL FOR ALL FILES
L68         38398 S L36 (100A) L40
L69          2549 FILE USPATFULL
L70          1600 FILE PCTFULL
L71            53 FILE JAPIO
     TOTAL FOR ALL FILES
L72          4202 S L68 (100A) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN OR OINTM
L73             1 FILE USPATFULL
L74             2 FILE PCTFULL
L75             0 FILE JAPIO
     TOTAL FOR ALL FILES
L76             3 S L72 (100A) (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCO
L77           221 FILE USPATFULL
L78           172 FILE PCTFULL
L79             5 FILE JAPIO
     TOTAL FOR ALL FILES
L80           398 S  ( FR-900520 OR ASCOMYCIN )
L81           157 FILE USPATFULL
L82           105 FILE PCTFULL
L83             0 FILE JAPIO
     TOTAL FOR ALL FILES
L84           262 S L80 AND L36
L85             5 FILE USPATFULL
L86            38 FILE PCTFULL
L87             0 FILE JAPIO
     TOTAL FOR ALL FILES
L88            43 S L80 (4S) L36
L89             5 FILE USPATFULL
L90            35 FILE PCTFULL
L91             0 FILE JAPIO
     TOTAL FOR ALL FILES
L92            40 S L80 (3S) L36
L93            21 FILE USPATFULL
L94             9 FILE PCTFULL
L95             0 FILE JAPIO
     TOTAL FOR ALL FILES
L96            30 S  ( FR-900520 OR ASCOMYCIN )/AB
L97            23 FILE USPATFULL
L98            23 FILE PCTFULL
L99             0 FILE JAPIO
     TOTAL FOR ALL FILES
```

```
L100          46 S  ( FR-900520 OR ASCOMYCIN )/CLM
L101          14 FILE USPATFULL
L102           9 FILE PCTFULL
L103           0 FILE JAPIO
     TOTAL FOR ALL FILES
L104          23 S L100 AND L36
L105           1 FILE USPATFULL
L106           4 FILE PCTFULL
L107           0 FILE JAPIO
     TOTAL FOR ALL FILES
L108           5 S L100 AND L44
L109         299 FILE USPATFULL
L110         605 FILE PCTFULL
L111           0 FILE JAPIO
     TOTAL FOR ALL FILES
L112         904 S (RAPAMYCIN OR FK-506 OR TACROLIMUS) AND L44
L113           6 FILE USPATFULL
L114          17 FILE PCTFULL
L115           0 FILE JAPIO
     TOTAL FOR ALL FILES
L116          23 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/AB AND L44
L117          41 FILE USPATFULL
L118          96 FILE PCTFULL
L119           0 FILE JAPIO
     TOTAL FOR ALL FILES
L120         137 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/CLM AND L44
L121           2 FILE USPATFULL
L122          13 FILE PCTFULL
L123           0 FILE JAPIO
     TOTAL FOR ALL FILES
L124          15 S L116 AND L120
L125      310100 FILE USPATFULL
L126       66581 FILE PCTFULL
L127       60000 FILE JAPIO
     TOTAL FOR ALL FILES
L128      436681 S PETROLATUM OR (PARAFFIN) OR (MICROCRYSTALLINE WAX) OR (MICROC
L129       13150 FILE USPATFULL
L130        5336 FILE PCTFULL
L131         632 FILE JAPIO
     TOTAL FOR ALL FILES
L132       19118 S L128 (1S) L36
L133        1719 FILE USPATFULL
L134        1241 FILE PCTFULL
L135          31 FILE JAPIO
     TOTAL FOR ALL FILES
L136        2991 S L68 (100A) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN)
L137      847317 FILE USPATFULL
L138      184690 FILE PCTFULL
L139      232069 FILE JAPIO
     TOTAL FOR ALL FILES
L140     1264076 S  (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN)
L141      385506 FILE USPATFULL
L142      137815 FILE PCTFULL
L143       76006 FILE JAPIO
     TOTAL FOR ALL FILES
L144      599327 S OINTMENT OR GEL OR TRANSDERM? OR LOTION OR CREAM OR SALVE? OR
L145        1645 FILE USPATFULL
L146        2750 FILE PCTFULL
L147          35 FILE JAPIO
     TOTAL FOR ALL FILES
L148        4430 S L132 (5S) (L140 OR L144)
L149           2 FILE USPATFULL
L150          25 FILE PCTFULL
L151           0 FILE JAPIO
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     TOTAL FOR ALL FILES
L152          27 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/CLM AND L148
L153           1 FILE USPATFULL
L154           1 FILE PCTFULL
L155           0 FILE JAPIO
     TOTAL FOR ALL FILES
L156           2 S  ( FR-900520 OR ASCOMYCIN )/CLM AND L148
L157           1 FILE USPATFULL
L158           1 FILE PCTFULL
L159           0 FILE JAPIO
     TOTAL FOR ALL FILES
L160           2 S  ( FR-900520 OR ASCOMYCIN )/AB AND L148
L161         807 FILE USPATFULL
L162         688 FILE PCTFULL
L163          21 FILE JAPIO
     TOTAL FOR ALL FILES
L164        1516 S IMMUNOSUPRRESSANT? OR (IMMUNO(2W) SUPPRESS?)
L165        1645 FILE USPATFULL
L166        2750 FILE PCTFULL
L167          35 FILE JAPIO
     TOTAL FOR ALL FILES
L168        4430 S L132 (5S) (L140 OR L144)
L169           0 FILE USPATFULL
L170           2 FILE PCTFULL
L171           0 FILE JAPIO
     TOTAL FOR ALL FILES
L172           2 S L164 (2S) L168
                 SAVE ALL L09871367A/L

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     (FILE 'HOME' ENTERED AT 15:05:28 ON 12 FEB 2003)

     FILE 'USPATFULL, PCTFULL, JAPIO' ENTERED AT 15:05:52 ON 12 FEB 2003
L1         96958 FILE USPATFULL
L2         28525 FILE PCTFULL
L3          8744 FILE JAPIO
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L4        134227 S UREA OR (MONOACETYL(3A)UREA) OR (DODECYL (3A) UREA) OR (DIPHE
L5        101965 FILE USPATFULL
L6         29128 FILE PCTFULL
L7          2702 FILE JAPIO
     TOTAL FOR ALL FILES
L8        133795 S SODIUM CHLORIDE
L9          2163 FILE USPATFULL
L10          636 FILE PCTFULL
L11           78 FILE JAPIO
     TOTAL FOR ALL FILES
L12         2877 S ( MONO(1W)CARBOXYLIC(1W) ACID ) OR (CYCLIC(1W) CARBOXYLIC(1W)
L13        19583 FILE USPATFULL
L14         3498 FILE PCTFULL
L15         2064 FILE JAPIO
     TOTAL FOR ALL FILES
L16        25145 S ( MONOCARBOXYLIC ACID ) OR (CYCLICCARBOXYLIC ACID)
L17         1846 FILE USPATFULL
L18          558 FILE PCTFULL
L19           61 FILE JAPIO
     TOTAL FOR ALL FILES
L20         2465 S ( MONO-CARBOXYLIC ACID ) OR (CYCLIC-CARBOXYLIC ACID)
L21         1846 FILE USPATFULL
L22          558 FILE PCTFULL
L23           61 FILE JAPIO
     TOTAL FOR ALL FILES
L24         2465 S ( MONO CARBOXYLIC ACID ) OR (CYCLIC CARBOXYLIC ACID)
L25        20851 FILE USPATFULL
L26         3877 FILE PCTFULL
L27         2134 FILE JAPIO
     TOTAL FOR ALL FILES
L28        26862 S L12 OR L16 OR L24
L29        70706 FILE USPATFULL
L30        27871 FILE PCTFULL
L31         5837 FILE JAPIO
     TOTAL FOR ALL FILES
L32       104414 S LACTIC OR GLYCOLIC OR LACTATE OR (SODIUM (3A) (LACTATE OR LAC
L33       231523 FILE USPATFULL
L34        67838 FILE PCTFULL
L35        19197 FILE JAPIO
     TOTAL FOR ALL FILES
L36       318558 S L4 OR L8 OR L28 OR L32
L37       521097 FILE USPATFULL
L38       122461 FILE PCTFULL
L39       105728 FILE JAPIO
     TOTAL FOR ALL FILES
L40       749286 S PETROLATUM OR (PARAFFIN) OR (MICROCRYSTALLINE WAX) OR (MICROC
L41        30789 FILE USPATFULL
L42        19977 FILE PCTFULL
L43         1065 FILE JAPIO
     TOTAL FOR ALL FILES
L44        51831 S L36 (3S) L40
L45           14 FILE USPATFULL
L46           45 FILE PCTFULL
L47            0 FILE JAPIO
```

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     TOTAL FOR ALL FILES
L48            59 S L44 AND ASCOMYCIN
L49          3003 FILE USPATFULL
L50          9790 FILE PCTFULL
L51            55 FILE JAPIO
     TOTAL FOR ALL FILES
L52         12848 S L44 (5S) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN OR OINTMEN
L53           136 FILE USPATFULL
L54           690 FILE PCTFULL
L55             0 FILE JAPIO
     TOTAL FOR ALL FILES
L56           826 S L52 AND (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCOMYC
L57            31 FILE USPATFULL
L58           242 FILE PCTFULL
L59             0 FILE JAPIO
     TOTAL FOR ALL FILES
L60           273 S L52 AND ( FK-506 OR FR-900520 OR ASCOMYCIN )
L61             1 FILE USPATFULL
L62           103 FILE PCTFULL
L63             0 FILE JAPIO
     TOTAL FOR ALL FILES
L64           104 S L52 (3S) (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCOMY
L65         28450 FILE USPATFULL
L66          8904 FILE PCTFULL
L67          1044 FILE JAPIO
     TOTAL FOR ALL FILES
L68         38398 S L36 (100A) L40
L69          2549 FILE USPATFULL
L70          1600 FILE PCTFULL
L71            53 FILE JAPIO
     TOTAL FOR ALL FILES
L72          4202 S L68 (100A) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN OR OINTM
L73             1 FILE USPATFULL
L74             2 FILE PCTFULL
L75             0 FILE JAPIO
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L76             3 S L72 (100A) (IMMUNOSUPPRESSANT? OR FK-506 OR FR-900520 OR ASCO
L77           221 FILE USPATFULL
L78           172 FILE PCTFULL
L79             5 FILE JAPIO
     TOTAL FOR ALL FILES
L80           398 S  ( FR-900520 OR ASCOMYCIN )
L81           157 FILE USPATFULL
L82           105 FILE PCTFULL
L83             0 FILE JAPIO
     TOTAL FOR ALL FILES
L84           262 S L80 AND L36
L85             5 FILE USPATFULL
L86            38 FILE PCTFULL
L87             0 FILE JAPIO
     TOTAL FOR ALL FILES
L88            43 S L80 (4S) L36
L89             5 FILE USPATFULL
L90            35 FILE PCTFULL
L91             0 FILE JAPIO
     TOTAL FOR ALL FILES
L92            40 S L80 (3S) L36
L93            21 FILE USPATFULL
L94             9 FILE PCTFULL
L95             0 FILE JAPIO
     TOTAL FOR ALL FILES
L96            30 S  ( FR-900520 OR ASCOMYCIN )/AB
L97            23 FILE USPATFULL
L98            23 FILE PCTFULL
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L99           0 FILE JAPIO
     TOTAL FOR ALL FILES
L100         46 S  ( FR-900520 OR ASCOMYCIN )/CLM
L101         14 FILE USPATFULL
L102          9 FILE PCTFULL
L103          0 FILE JAPIO
     TOTAL FOR ALL FILES
L104         23 S L100 AND L36
L105          1 FILE USPATFULL
L106          4 FILE PCTFULL
L107          0 FILE JAPIO
     TOTAL FOR ALL FILES
L108          5 S L100 AND L44
L109        299 FILE USPATFULL
L110        605 FILE PCTFULL
L111          0 FILE JAPIO
     TOTAL FOR ALL FILES
L112        904 S (RAPAMYCIN OR FK-506 OR TACROLIMUS) AND L44
L113          6 FILE USPATFULL
L114         17 FILE PCTFULL
L115          0 FILE JAPIO
     TOTAL FOR ALL FILES
L116         23 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/AB AND L44
L117         41 FILE USPATFULL
L118         96 FILE PCTFULL
L119          0 FILE JAPIO
     TOTAL FOR ALL FILES
L120        137 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/CLM AND L44
L121          2 FILE USPATFULL
L122         13 FILE PCTFULL
L123          0 FILE JAPIO
     TOTAL FOR ALL FILES
L124         15 S L116 AND L120
L125     310100 FILE USPATFULL
L126      66581 FILE PCTFULL
L127      60000 FILE JAPIO
     TOTAL FOR ALL FILES
L128     436681 S PETROLATUM OR (PARAFFIN) OR (MICROCRYSTALLINE WAX) OR (MICROC
L129      13150 FILE USPATFULL
L130       5336 FILE PCTFULL
L131        632 FILE JAPIO
     TOTAL FOR ALL FILES
L132      19118 S L128 (1S) L36
L133       1719 FILE USPATFULL
L134       1241 FILE PCTFULL
L135         31 FILE JAPIO
     TOTAL FOR ALL FILES
L136       2991 S L68 (100A) (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN)
L137     847317 FILE USPATFULL
L138     184690 FILE PCTFULL
L139     232069 FILE JAPIO
     TOTAL FOR ALL FILES
L140    1264076 S  (TOPICAL OR EXTERNAL OR EPIDERMAL OR SKIN)
L141     385506 FILE USPATFULL
L142     137815 FILE PCTFULL
L143      76006 FILE JAPIO
     TOTAL FOR ALL FILES
L144     599327 S OINTMENT OR GEL OR TRANSDERM? OR LOTION OR CREAM OR SALVE? OR
L145       1645 FILE USPATFULL
L146       2750 FILE PCTFULL
L147         35 FILE JAPIO
     TOTAL FOR ALL FILES
L148       4430 S L132 (5S) (L140 OR L144)
L149          2 FILE USPATFULL
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L150         25 FILE PCTFULL
L151          0 FILE JAPIO
     TOTAL FOR ALL FILES
L152         27 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)/CLM AND L148
L153          1 FILE USPATFULL
L154          1 FILE PCTFULL
L155          0 FILE JAPIO
     TOTAL FOR ALL FILES
L156          2 S  ( FR-900520 OR ASCOMYCIN )/CLM AND L148
L157          1 FILE USPATFULL
L158          1 FILE PCTFULL
L159          0 FILE JAPIO
     TOTAL FOR ALL FILES
L160          2 S  ( FR-900520 OR ASCOMYCIN )/AB AND L148
L161        807 FILE USPATFULL
L162        688 FILE PCTFULL
L163         21 FILE JAPIO
     TOTAL FOR ALL FILES
L164       1516 S IMMUNOSUPRRESSANT? OR (IMMUNO(2W) SUPPRESS?)
L165       1645 FILE USPATFULL
L166       2750 FILE PCTFULL
L167         35 FILE JAPIO
     TOTAL FOR ALL FILES
L168       4430 S L132 (5S) (L140 OR L144)
L169          0 FILE USPATFULL
L170          2 FILE PCTFULL
L171          0 FILE JAPIO
     TOTAL FOR ALL FILES
L172          2 S L164 (2S) L168
                SAVE ALL L09871367A/L
L173       2319 FILE USPATFULL
L174       2486 FILE PCTFULL
L175         53 FILE JAPIO
     TOTAL FOR ALL FILES
L176       4858 S (RAPAMYCIN OR FK-506 OR TACROLIMUS)

     FILE 'CAPLUS, USPATFULL, PCTFULL, JAPIO' ENTERED AT 16:34:08 ON 12 FEB
     2003
L177       6382 FILE CAPLUS
L178       2358 FILE USPATFULL
L179       2519 FILE PCTFULL
L180         57 FILE JAPIO
     TOTAL FOR ALL FILES
L181      11316 S L176 OR L80
L182        136 FILE CAPLUS
L183        246 FILE USPATFULL
L184        392 FILE PCTFULL
L185          3 FILE JAPIO
     TOTAL FOR ALL FILES
L186        777 S L181 (3S) L144
L187         48 FILE CAPLUS
L188        122 FILE USPATFULL
L189        178 FILE PCTFULL
L190          1 FILE JAPIO
     TOTAL FOR ALL FILES
L191        349 S L186 AND OINTMENT
L192     191354 FILE CAPLUS
L193     302831 FILE USPATFULL
L194     109892 FILE PCTFULL
L195      41115 FILE JAPIO
     TOTAL FOR ALL FILES
L196     645192 S (ENHANC? OR PROMOT? OR INCREAS? OR IMPROV?) (1S) (PENETRAT? O
L197          5 FILE CAPLUS
L198         27 FILE USPATFULL
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L199          87 FILE PCTFULL
L200           0 FILE JAPIO
     TOTAL FOR ALL FILES
L201         119 S L196 AND L191

     FILE 'REGISTRY' ENTERED AT 16:43:38 ON 12 FEB 2003
L202           1 S PROPYLENE CARBONATE/CN
L203           1 S DIISOPROPYL ADIPATE/CN

     FILE 'CAPLUS, USPATFULL, PCTFULL, JAPIO' ENTERED AT 16:45:53 ON 12 FEB
     2003
L204           0 FILE CAPLUS
L205           0 FILE USPATFULL
L206           0 FILE PCTFULL
L207           0 FILE JAPIO
     TOTAL FOR ALL FILES
L208           0 S DIETHYL SEBACATE/CN
L209         282 FILE CAPLUS
L210         724 FILE USPATFULL
L211         183 FILE PCTFULL
L212          23 FILE JAPIO
     TOTAL FOR ALL FILES
L213        1212 S DIETHYL SEBACATE

     FILE 'REGISTRY' ENTERED AT 16:53:06 ON 12 FEB 2003
L214           1 S DIETHYL SEBACATE/CN
L215           0 S L196 (2S) L36

     FILE 'CAPLUS, USPATFULL, PCTFULL, JAPIO' ENTERED AT 16:57:53 ON 12 FEB
     2003
L216        2755 FILE CAPLUS
L217        3338 FILE USPATFULL
L218        6876 FILE PCTFULL
L219         133 FILE JAPIO
     TOTAL FOR ALL FILES
L220       13102 S L196 (2S) L36
L221           4 FILE CAPLUS
L222          60 FILE USPATFULL
L223         295 FILE PCTFULL
L224           0 FILE JAPIO
     TOTAL FOR ALL FILES
L225         359 S L220 AND L181
L226           0 FILE CAPLUS
L227          15 FILE USPATFULL
L228          36 FILE PCTFULL
L229           0 FILE JAPIO
     TOTAL FOR ALL FILES
L230          51 S L220 AND L80
L231           0 FILE CAPLUS
L232           6 FILE USPATFULL
L233          57 FILE PCTFULL
L234           0 FILE JAPIO
     TOTAL FOR ALL FILES
L235          63 S L220 AND L181/CLM

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L82 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:497327 CAPLUS
DOCUMENT NUMBER: 117:97327
TITLE: Pharmaceutical compositions containing tricyclic compounds
INVENTOR(S): **Asakura, Sotoo**; Fukae, Michiyo; Nakanishi, Shigeo; Koyama, Yasuto; Kiyota, Youhei
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 483842	A1	19920506	EP 1991-118592	19911031
EP 483842	B1	19941214		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 9108388	A	19920826	ZA 1991-8388	19911021
CA 2054629	AA	19920503	CA 1991-2054629	19911031
AU 9186922	A1	19920507	AU 1991-86922	19911031
AU 655603	B2	19950105		
HU 60924	A2	19921130	HU 1991-3438	19911031
HU 217540	B	20000228		
JP 05009117	A2	19930119	JP 1991-313423	19911031
ES 2064856	T3	19950201	ES 1991-118592	19911031
CN 1061153	A	19920520	CN 1991-110545	19911101
CN 1069194	B	20010808		
RU 2084222	C1	19970720	RU 1991-5010231	19911101
US 5955469	A	19990921	US 1994-280137	19940725

PRIORITY APPLN. INFO.: JP 1990-298135 A 19901102
JP 1990-298136 A 19901102
US 1991-786782 B1 19911101
OTHER SOURCE(S): MARPAT 117:97327

L82 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:455982 CAPLUS
DOCUMENT NUMBER: 117:55982
TITLE: Suspensions containing tricyclic or related compounds for oral or ocular use
INVENTOR(S): **Asakura, Sotoo**; Koyama, Yasuto; Kiyota, Youhei; Akashi, Kiyoko; Kagayama, Akira; Murakami, Yoshio; Nakate, Toshiomi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 484936	A1	19920513	EP 1991-118982	19911107
EP 484936	B1	19941005		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2054983	AA	19920509	CA 1991-2054983	19911105
RU 2079304	C1	19970520	RU 1991-5010186	19911106
AU 9187099	A1	19920514	AU 1991-87099	19911107

AU 653556	B2	19941006			
ZA 9108846	A	19920826	ZA 1991-8846		19911107
HU 60925	A2	19921130	HU 1991-3507		19911107
HU 210760	B	19950728			
ES 2061149	T3	19941201	ES 1991-118982		19911107
CN 1061907	A	19920617	CN 1991-110733		19911108
CN 1069195	B	20010808			
JP 05155770	A2	19930622	JP 1991-293148		19911108
JP 2581359	B2	19970212			
IL 100011	A1	19951208	IL 1991-100011		19911108
US 5368865	A	19941129	US 1993-97617		19930727
US 5496564	A	19960305	US 1994-296403		19940826
PRIORITY APPLN. INFO.:			JP 1990-304839	A	19901108
			GB 1991-4834	A	19910307
			JP 1991-259358	A	19911007
			US 1991-788041	B1	19911105
			US 1993-97617	A1	19930727

OTHER SOURCE(S): MARPAT 117:55982

L82 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:241941 CAPLUS
DOCUMENT NUMBER: 116:241941
TITLE: Ointments containing tricyclic compounds for treatment of skin diseases
INVENTOR(S): **Asakura, Sotoo**; Murakami, Yoshio; Kanagawa, Nobuto; Nakate, Toshiomi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 474126	A1	19920311	EP 1991-114598	19910830
EP 474126	B1	19970319		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 9183515	A1	19920312	AU 1991-83515	19910830
AU 656145	B2	19950127		
AT 150304	E	19970415	AT 1991-114598	19910830
ES 2099112	T3	19970516	ES 1991-114598	19910830
HU 59002	A2	19920428	HU 1991-2846	19910903
ZA 9106983	A	19920527	ZA 1991-6983	19910903
RU 2079303	C1	19970520	RU 1991-5001707	19910903
CA 2050623	AA	19920305	CA 1991-2050623	19910904
CN 1059468	A	19920318	CN 1991-108796	19910904
CN 1069193	B	20010808		
JP 05017481	A2	19930126	JP 1991-224418	19910904
JP 2526752	B2	19960821		
US 5385907	A	19950131	US 1993-62330	19930517
PRIORITY APPLN. INFO.:			JP 1990-235177 A	19900904
			US 1991-750942 B1	19910828

OTHER SOURCE(S): MARPAT 116:241941

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ACCESSION NUMBER: 1991:150214 CAPLUS
DOCUMENT NUMBER: 114:150214
TITLE: Aqueous liquid compositions containing dioxaazatricyclooctacosenetetraones
INVENTOR(S): Honbo, Toshiyasu; Tanimoto, Sachiyo; Yoshida, Hiromitsu; Hata, Takehisa; **Asakura, Sotoo**; Koyama, Yasuto; Kiyota, Youhei

PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 406791	A2	19910109	EP 1990-112655	19900703
EP 406791	A3	19911106		
EP 406791	B1	19950201		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 9058642	A1	19910124	AU 1990-58642	19900703
AU 635286	B2	19930318		
ZA 9005202	A	19910424	ZA 1990-5202	19900703
ES 2066915	T3	19950316	ES 1990-112655	19900703
CA 2020431	AA	19910106	CA 1990-2020431	19900704
IL 94971	A1	19951208	IL 1990-94971	19900704
CN 1048496	A	19910116	CN 1990-103445	19900705
CN 1063322	B	20010321		
JP 03128320	A2	19910531	JP 1990-178974	19900705
JP 2536248	B2	19960918		
US 5770607	A	19980623	US 1994-276495	19940718

PRIORITY APPLN. INFO.: JP 1989-176637 A 19890705
US 1990-546883 B1 19900702
US 1992-853020 B1 19920318

OTHER SOURCE(S): MARPAT 114:150214

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PATENT INFORMATION:	US 6124362	20000926	
APPLICATION INFO.:	US 1999-353408	19990715	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-93285P	

SUMM Immunosuppressive compounds whose immunosuppressive activity derives principally or in significant part from their direct or indirect inhibition of IL-2 gene transcription (e.g., corticosteroids, **ascomycins**, and cyclosporins; in particular cyclosporin A, FK506, and their various immunosuppressive derivatives and analogues;' especially compounds which are at at least as active as cyclosporin A in an IL-2 reporter gene assay) are hereinafter referred to as "IL-2 transcription inhibitors".

SUMM The carrier medium may further comprise a surfactant, for example as described above, or a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer known, for example, under the trade names Pluronic or Poloxamer, e.g. Poloxamer 188; an ethoxylated cholesterin for example Solulan C24; a vitamin derivative, e.g. tocopherol **polyethylene** glycol succinate; sodium dodecylsulfate or sodium laurylsulfate; a bile acid or salt thereof, for example cholic acid, **glycolic** acid or a salt, e.g. sodium cholate; or lecithin. If present in the solid dispersion, the surfactant is generally in an amount of up to 20% by weight based on the total weight of the composition, e.g. 1 to 15% by weight. Other pharmaceutically acceptable excipients, e.g as described above, may be included in the solid dispersion as desired. When formulated as a solid dispersion, the compositions of this invention may be administered, for example, in tablet, capsule, granule or powder form, e.g. in a sachet.

ACCESSION NUMBER: 2001:79149 USPATFULL
TITLE: Pharmaceutical compositions for the treatment of transplant rejection or autoimmune or inflammatory conditions comprising cyclosporin A and 40-0-(2-hydroxyethyl)-rapamycin

INVENTOR(S): Zenke, Gerhard, Rheinfelden, Germany, Federal Republic of
Schuurman, Hendrik, Basel, Switzerland
Haeberlin, Barbara, Riehen, Switzerland
Meinzer, Armin, Buggingen, Germany, Federal Republic of
PATENT ASSIGNEE(S): Novartis AG, Basel, Switzerland (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6239124	B1	20010529	
	WO 9804279		19980205	
APPLICATION INFO.:	US 1999-230618		19990128	(9)
	WO 1997-EP4123		19970729	
			19990128	PCT 371 date
			19990128	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1996-15942	19960730
	GB 1997-5684	19970319

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Weddington, Kevin E.
LEGAL REPRESENTATIVE: Lopez, Gabriel, Furman, Diane E.
NUMBER OF CLAIMS: 20

L48 ANSWER 13 OF 59 USPATFULL

SUMM Among the polyols which are useful as a vehicle herein are linear and branched chain alkyl polyhdyroxyl compounds. Preferred polyols include propylene glycol, sugars having up to about 12 carbons atoms, sugar alcohols having up to about 12 carbon atoms, and mixtures thereof, glycerin, polypropylene glycols, **polyethylene** glycols, ethyl hexane diol, hexylene glycols, **ureas** and mixtures thereof.

SUMM Specific examples of useful polyols include materials such as **urea**; guanidine; **glycolic** acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); **lactic** acid and **lactate** salts (e.g. ammonium and quaternary alkyl ammonium); sucrose, fructose, glucose, eruthrose, erythritol, sorbitol, mannitol, glycerol, hexanetriol, propylene glycol, butylene glycol, hexylene glycol, and the like; **polyethylene** glycols such as PEG-2, PEG-3, PEG-30, PEG-50, polypropylene glycols such as PPG-9, PPG-12, PPG-15, PPG-17, PPG-20, PPG-26, PPG-30, PPG-34; alkoxylated glucose; hyaluronic acid; and mixtures thereof. Also useful are materials such as aloe vera in any of its variety of forms (e.g., aloe vera gel), chitin, starch-grafted sodium polyacrylates such as Sanwet (RTM) IM-1000, IM-1500, and IM-2500 (available from Celanese Superabsorbent Materials, Portsmouth, Va.); **lactamide** monoethanolamine; acetamide monoethanolamine; and mixtures thereof. Also useful are propoxylated glycerols as described in propoxylated glycerols described in U.S. Pat. No. 4,976,953, to Orr et al., issued Dec. 11, 1990, which is incorporated by reference herein in its entirety.

SUMM Other classes of optional activity enhancers for use herein include flavinoids, **ascomycin** derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Pat. No. 5,529,769, JP 10017431, WO 95/35103, U.S. Pat. No. 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Pat. No. 5,631,282, U.S. Pat. No. 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al, published Sep. 8, 1993 and WO 97/01346 to Bonte et al, published Jan. 16, 1997 (both of which are herein incorporated by reference in their entirety), proeoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Pat. No. 5,015,470, issued May 14, 1991, U.S. Pat. No. 5,300,284, issued Apr. 5, 1994 and U.S. Pat. No. 5,185,325, issued Feb. 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promotors, analogs or inhibitors such as interleukin1 inhibitors, interleukin-6 inhibitors, interleukin-10 promoters, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interfuron agonists and antagonists, hydroxyacids such as those described in U.S. Pat. No. 5,550,158, benzophenones and hydantoin anticonvulsants such as phenytoin.

ACCESSION NUMBER: 2000:128394 USPATFULL
TITLE: Method for regulating hair growth
INVENTOR(S): Bradbury, Barton James, West Chester, OH, United States
Soper, Shari Joy, Cincinnati, OH, United States
Kaczvinsky, Jr., Joseph Robert, Cincinnati, OH, United States
Bailey, Dorothy Limerick, Fairfield, OH, United States
Gale, Celeste Dawn, Hamilton, OH, United States
PATENT ASSIGNEE(S): The Procter & Gamble Company, Cincinnati, OH, United States (U.S. corporation)

NUMBER	KIND	DATE

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DETD The first evidence suggesting efficacy for the treatment of inflammatory skin disorders with immunosuppressants came from the systemic administration of cyclosporin A to psoriatic patients. Although its use is fraught with nephro- and hepatic toxicity, cyclosporin A has been employed in the treatment of many inflammatory skin disorders. Recently, it has been demonstrated that topical application of immunosuppressants, such as **FK-506**, was effective in inhibiting skin inflammatory reactions in an allergic contact dermatitis model. Other immunosuppressants, such as corticosteroids (see, e.g., American Medical Association (1992) Drug Evaluations (Subscriptions), Section 1), azathioprine (Imuran.RTM.), bromocriptine (Parlodel.RTM.), chlorambucil (Leukeran.RTM.), colchicine, cyclophosphamide (Cytoxan.RTM. or Neosar.RTM.), cyclosporine (Sandimmune.RTM.), dapsone, methotrexate (Folex.RTM. or Mexate.RTM.), and fluorouracil (Adrucil.RTM.); rapamycin; and FK-520-like macrolide antibiotics will also find use in the methods of this invention.

DETD A loperamide **ointment** was prepared containing, in percent by weight, Miglyol.TM. 840-B **Gel** (10.0%), Eutanol G-Octyldodecanol (17.0%), Cril 6-Glyceryl isostearate (3.0%), hard **paraffin** wax (3.0%), zinc stearate (1.0%), Amphisol K (0.5%), Germaben II (1.0%), magnesium sulfate (0.2%), **urea** (10.0%), loperamide (2.0%) with water making up the remainder.

ACCESSION NUMBER: 1999:121379 USPATFULL
TITLE: Screening methods for cytokine inhibitors
INVENTOR(S): Mak, Vivian, Menlo Park, CA, United States
PATENT ASSIGNEE(S): Adolor Corporation, Malvern, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5962477		19991005
APPLICATION INFO.:	US 1998-9		

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DETD Still further treatments for which the invention dithiocarbamate-containing composition(s), which, when activated, are advantageously effective as nitric oxide scavenger(s), are employed as nitric oxide scavenger(s) in conjunction with the primary treating agent include administration of agents for the treatment of multiple sclerosis, such as 4-aminopyridine, deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC), anti-cytokine monoclonal antibodies, anti-inflammatory agents, bacloten, bethanechol chloride, carbamazepine, carbohydrate drugs, clonazepam, CNS and immune system function modulators, cyclophosphamide, cyclosporine A, cytokines (e.g., IFN-.alpha., alfaferone, IFN-.beta. 1b, betaseron, TGF-.beta.2, PEG-TGF-.beta.2, betakine, IFN-.beta./Rebif, frone, interferon-.beta., IFN-.beta., and the like), CD4+T cell inhibitors (e.g., AnergiX), CD28 antagonists, growth factors (e.g., glial growth factor, GGF, nerve growth factors, TGF-.beta.2, PEG-TGF-.beta.2, betakine, and the like), humanized MAb (e.g., anti-IFN-.gamma.MAb, smart anti-IFN-.gamma.MAb, anti-Tac antibody, smart anti-Tac antibody, and the like), humanized anti-CD4 MAb (e.g., anti-CD4 MAb, centara, and the like), hydrolase stimulants (e.g., castanospermine), IFN-.alpha., IFN-.gamma. antagonists (e.g., anti-IFN-.gamma.MAb, smart anti-IFN.gamma.MAb, and the like), IL-2 antagonists (e.g., tacrolimus, Fujimycin, Prograf, IL-2 fusion toxin, DAB.sub.389 IL-2, and the like), IL-4 antagonists (e.g., IL-4 fusion toxin, DAB.sub.389 IL-4, and the like), immune-mediated neuronal damage inhibitors, immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ET-18- OCH-3, ET-18-OME, and the like), immunosuppressants (e.g., azathioprine, castanospermine, tacrolimus, **FK-506**, Fujimycin, Prograf, anti-leukointegrin MAb, primatized anti-CD4 antibody, linomide, roquinimex, transcyclo-pentanyl purine analogs, spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCl, cyclosporine, SandImmune, IL-10, anti-TCR MAbs, anti-CD4 MAb, cantara, immunophilins, cyclophosphamide, and the like), integrin antagonists (e.g., anti-integrin monoclonal antibodies), interferon agonists, interferon-.beta.-1b, isoprinosine, IV methylprednisolone, macrolides, MAO B inhibitors (e.g., selegiline, Parkinyl, and the like), methotrexate, mitoxantrone, muscarinic antagonists, oxybutinin chloride, oxygen free radical antagonists (e.g., tetrandrine, biobenzylisoquinoline alkaloid, and the like), phenoxybenzamine, phospholipase C inhibitors, photodynamic therapies (e.g., benzoporphyrin derivative (BPD)), platelet activating factor antagonists (e.g., ginkgolide B), potassium channel antagonists (e.g., aminodiaquine), propranolol, prostaglandin synthase inhibitors (e.g., sulfasalazine, salazosulfa-pyridine, azulfidine, salazopyrin, and the like), protease antagonists (e.g., ginkgolide B), recombinant soluble IL-1 receptors, spergualin analogs (e.g., spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCl, and the like), selectin antagonists (e.g., lectin-1, recombinant IML-1, and the like), soluble TNF receptor I, TNF antagonists (e.g., thalidomide, TNF inhibitors, and the like), and the like.

DETD Additional treatments for which the invention dithiocarbamate-containing composition(s), which, when activated, are advantageously effective as nitric oxide scavenger(s) are employed as nitric oxide scavenger(s) in conjunction with the primary treating agent include administration of organ transplantation agents, such as anti-CD25 MAbs, anti-Tac antibodies, anti-TNF MAb, apoptosin, azathioprines (e.g., imuran), complement inhibiting factors (e.g., CD59), cyclosporines (e.g., CsA), **FK-506**/rapamycin binding proteins (FKBP), glucocorticoids, humanized version of OKT3 (e.g., huOKT3-185), hydroorotate dehydrogenase inhibitors (e.g., Brequinar), orthoclone OKT3 (e.g., IgG2a anti-T cell murine monoclonal antibody, muromonab-CD3, and the like), rapamycins, streptomyces isolates, and the like.

DETD Additional treatments for which the invention dithiocarbamate-containing composition(s) are advantageously employed nitric oxide scavenger(s) in

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SUMM . . . Pharmaceutical compositions under 6 above also include compositions suitable for topical administration e.g., in the form of a dermal cream, **ointment**, gel or like preparation, especially in combination or association with **penetration enhancing** agents, e.g., for the treatment of autoimmune or inflammatory conditions of the skin, as well as composition in the form. . .

SUMM Pharmaceutical compositions under 6 above, e.g., for oral administration, are suitably **emulsions**, microemulsions, **emulsion** preconcentrates or microemulsion preconcentrates, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, comprising the IL-2 transcription inhibitor (e.g., cyclosporin A or FK506, especially cyclosporin A) and 40-O-(2-hydroxyethyl)-**rapamycin** in a synergistic ratio.

SUMM . . . The capsule shells may be soft or hard gelatine capsule shells. Stable soft gelatin capsules containing for example the cyclosporin A/40-O-(2-hydroxyethyl)-**rapamycin** compositions of this invention may be prepared in accordance with the method described in GB 2 282 586, the contents. . . the pharmaceutical compositions may be in drink solution form and may include water or any other aqueous system, to provide **emulsion** or microemulsion systems suitable for drinking.

DETD . . . by coadministration with Cyclosporin A; on the other hand, the disposition of Cyclosporin A is not affected by 40-O-(2-hydroxyethyl)-rapamycin. The **increase** of blood levels of 40-O-(2-hydroxyethyl)-rapamycin (two-fold) observed after oral coadministration with Cyclosporin may be attributed to the decrease in clearance and volume of distribution, whereas the two-fold **increase** of Cyclosporin blood levels after oral coadministration with 40-O-(2-hydroxyethyl)-rapamycin may be attributed to a higher **absorption**.

PI US 6239124 B1 20010529
WO 9804279 19980205

19960730

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DETD Examples of substances which may be used as **penetration enhancers** in the illustrated formulations include the following: ethanol; oleyl alcohol; alkylene polyols; oleic acids; **urea**; pyrrolidones; surfactants such as sodium lauryl sulfate; vegetable oil PEG-6 complexes such as the commercially available Labrafils (Gattefosse, Elmsford, N.Y);. . .

DETD . . . topical formulation in order to potentially enhance efficacy include, but are not limited to, the following: azathioprine; cyclophosphamide; the macrolide **FK-506**; deoxyspergualin; bredinin; didemnin B; methotrexate; and thalidomide.

CLM What is claimed is:

9. A method according to claim 6, wherein the **penetration enhancer** is selected from the group consisting of ethanol; oleyl alcohol; alkylene polyols; oleic acids; **urea**; pyrrolidones; surfactants; vegetable oil PEG-6 complexes; caprylic triglyceride; capric trrglyceride; glyceryl caprylate; glyceryl caprate; PEG-8 caprylate; PEG-8 caprate; ethoxydiglycol; and. . .

PI US 4996193 19910226

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SUMM Immunosuppression has been achieved by inhibiting a variety of enzymes including for example, the phosphatase calcineurin (inhibited by cyclosporin and **FK-506**); dihydroorotate dehydrogenase, an enzyme involved in the biosynthesis of pyrimidines (inhibited by leflunomide and brequinar); the kinase FRAP (inhibited by **rapamycin**); and the heat shock protein hsp70 (inhibited by deoxyspergualin). [See B. D. Kahan, Immunological Reviews, 136, pp. 29-49 (1993); R.. . .

SUMM . . . to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH, such as MPA or **rapamycin**, may be useful in preventing restenosis or other hyperproliferative vascular diseases [C. R. Gregory et al., Transplantation, 59, pp. 655-61. . .

SUMM . . . refers to a compound or drug which possesses immune response inhibitory activity. Examples of such agents include cyclosporin A, FK506, **rapamycin**, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG and mizoribine.

SUMM . . . the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug **delivery** systems (SEDDS) such as d.alpha.-tocopherol polyethyleneglycol 1000 succinate, or other similar polymeric **delivery** matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride. . . mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, **sodium chloride**, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol. . . chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-.beta.-cyclodextrins, or other solubilized derivatives may also be advantageously used to **enhance delivery** of compounds of formulae I-V.

SUMM . . . invention comprise an additional immunosuppression agent. Examples of additional immunosuppression agents include, but are not limited to, cyclosporin A, FK506, **rapamycin**, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG and mizoribine.

PI US 5807876 19980915

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AB . . . provides methods and formulations for site-specific immune suppression of immune/inflammatory responses with localized or topical application of immunosuppressants including cyclosporines, **rapamycins** (RPM), or combinations of immunosuppressants and anti-inflammatory compounds. Methods for the use of said formulations to effect site-specific immune suppression. . .

SUMM . . . cell expression. (See, e.g., A. D. Hess, et al., Transpl. Proc. 29 (1988).) Cyclosporines and other similar immunosuppressants such as **rapamycins**, **FK-506** derivatives and immunophilin binding agent have novel immunosuppressive properties compared to conventional agents: they are selective in their mechanism of. . . can be achieved in various models. Therefore, it would be extremely advantageous and desirable to develop topical formulations of cyclosporines, **rapamycins** and other immunosuppressants for localized tissue site-specific action.

SUMM . . . most pharmaceutical preparations, the scope of this invention is not limited to this one type of cyclosporine. Likewise, the terms " **rapamycin**", "RAP", "RPM", "**rapamycin** derivatives", and "**rapamycin** prodrugs" may be considered interchangeable with

the term "**rapamycin**(s)" throughout this disclosure. Similarly, the terms "steroid", "anti-inflammatory hormone", "corticosteroid anti-inflammatory", "corticosteroid", "glucocorticoid anti-inflammatory", "glucocorticoid", "steroid anti-inflammatory" and "steroid immunosuppressant". . .

SUMM . . . formulations of immunosuppressants, particularly those that react with immunophilin cytosolic binding proteins, which include but are not limited to cyclosporines, **rapamycins**, **FK 506** derivatives and prodrugs, and combinational immunosuppressants. There is also a need for a method for utilizing same, in the prevention. . .

SUMM . . . of action is not completely known. However, such immunosuppressants derived from microorganisms including the cyclosporines, and macrolides such as FK506, **Rapamycin** and derivatives possess common properties. They are lipophilic antibiotics that inhibit the transcription of T cell activation genes and/or signal. . .

SUMM . . . and targeting to specific tissue sites; and immune principles discovered that are necessary for inhibiting activated immune responses by cyclosporine, **rapamycin**, and other immunosuppressants during a disease state.

SUMM The present invention exploits observations that: 1) cyclosporine and **rapamycin** inhibit primary inflammatory/immune responses by local application using in vitro cellular site-specific models; 2) cyclosporine and **rapamycin** inhibit activated inflammatory/immune responses by local application using in vitro cellular site-specific models; 3) **rapamycin** is surprisingly efficacious with local application during both late and early inflammatory immune phases using in vitro cellular site-specific models;. . . to the late phase using in vitro cellular site-specific models; 5) consistent with these in vitro findings, either cyclosporine or **rapamycin** inhibit local inflammatory/immune responses by topical application to skin tissue using in vivo models of site-specific immune suppression; 6) this includes site-specific immune suppression effected by topical use of cyclosporine and **rapamycin** combinations in contact hypersensitivity reactions of skin tissue; 7) **rapamycin** is particularly efficacious during the late local inflammatory-immune phase in this latter example; 8) cyclosporine is particularly efficacious during the. . .

SUMM In accordance with another aspect of the present invention, there is provided a method for utilizing local **rapamycin** in a topical formulation for efficacious abrogation of skin hypersensitivity reactions, T-cell mediated immune processes, and inflammatory reactions. This method. . .

SUMM . . . aspect of the present invention, there is provided a method for utilizing local CsA in combination with a immunosuppressant agent, **rapamycin**, in a topical formulation for efficacious abrogation of skin hypersensitivity reactions, T-cell mediated immune processes, and inflammatory reactions. Novel combinations of immunosuppressive agents such as **rapamycin** and cyclosporine enable differential actions on immunoactivation pathways for potential synergism. This method should also prove effective in the clinical. . .

SUMM Examples of substances which may be used as **penetration enhancers** in the illustrated formulations include the following: ethanol; oleyl alcohol; alkylene polyols; oleic acids; **urea**; pyrrolidones; surfactants such as sodium lauryl sulfate; vegetable oil PEG-6 complexes such as the commercially available Labrafils (Gattefosse, Elmsford, N.Y.);. . .

DRWD . . . in combination with cyclosporine on topical immunosuppression: A) steroid combined with CsA in a dual skin graft model; and B) **rapamycin** alone and in combination with CsA in a skin contact dermatitis model.

DRWD . . . of either primary or activated in vitro models of cellular immune responses by varying concentrations of: A) cyclosporine, or B)

rapamycin.

DETD Topical formulations of cyclosporine, **rapamycin**, and other anti-inflammatory compounds have been successfully developed and tested in animal studies. They have been studied for transdermal penetration. . .

DETD cyclosporine-**rapamycin** synergism

DETD Topical **Rapamycin** (Alone without combination)--examples of site-specific in vitro models

DETD **Rapamycin** or CsA alone, provided potent site-specific immune suppression in either primary or activated cellular immune responses as in vitro models of local immune suppression. Cyclosporine or **rapamycin** inhibited primary inflammatory/immune responses by local application in mixed lymphocyte responses (FIGS. 14 A and B). **Rapamycin** was surprisingly efficacious with local application during both late and early inflammatory immune phases. Cyclosporine was particularly efficacious locally during. . .

DETD Consistent with these in vitro findings, either cyclosporine or **rapamycin** inhibited local inflammatory/immune responses by topical application to skin tissue undergoing hypersensitivity responses. This included site-specific immune suppression effected by topical use of cyclosporine and **rapamycin** combinations in contact hypersensitivity reactions of skin tissue (FIG. 13B). In FIG. 13B, **rapamycin**, alone, and in combination with CsA, provided new potent site-specific topical drugs in a mouse contact dermatitis model. **Rapamycin** (0.01%), cyclosporine (0.1%), and **rapamycin**-cyclosporine (0.01%/0.1%) combined formulations, were applied in a trinary drug delivery system consisting of 1,2 propanediol, diethylene glycol monoethyl ether, and. . .

DETD Similar to the in vitro data, **rapamycin** was particularly efficacious during the late local inflammatory-immune phase in this latter example, and cyclosporine was particularly efficacious during the early local inflammatory immune phase. **Rapamycin** (alone), at concentrations as low as 0.001%, provided surprising site-specific immune suppression. In addition, cyclosporine (0.01%) alone, was surprisingly efficacious using the particular delivery system detailed above. **Rapamycin** in combination with CsA (0.001%/0.01%), also provided unexpected site-specific immune suppression by topical application in this mouse contact dermatitis model. . .

DETD To further elaborate, **rapamycin** (0.001%), cyclosporine (0.01%), and **rapamycin**-cyclosporine (0.001%/0.01%) combined formulations, were applied in a trinary drug delivery system consisting of 1,2 propanediol, diethylene glycol monoethyl ether, and a glyceryl caprylate/caprate polyethylene glycol complex (6:3:1). **Rapamycin** derivatives and analogs, and other immunophilin binding macrolides and immunosuppressive agents shall similarly be effective using these methods and delivery. . .

DETD . . . invention provides a method and compositions for abrogating skin allograft rejection, hypersensitivity reactions, and inflammatory reactions. The use of cyclosporine, **rapamycin**, or combinations of immunosuppressant and other anti-inflammatory agents prolongs the survival of experimental skin allografts, and/or inhibits contact hypersensitivity inflammatory/immune. . . the present invention, however, circumvents these difficulties and provides a treatment methodology which effectively emphasizes the positive attributes of cyclosporine, **rapamycin**, and other immunosuppressants while minimizing the detrimental side effects.

CLM What is claimed is:

. . . composition of claim 1, further comprising an effective amount of one or more immunosuppressants selected from the group consisting of: **tacrolimus**, mizoribine, azathioprine, cyclophosphamide, deoxyspergualin, didemnin B, methotrexate, thalidomide, **rapamycin**, or combinations thereof.

. . . composition of claim 2, further comprising an effective amount of one

or more immunosuppressants selected from the group consisting of: **tacrolimus**, mizoribine, azathioprine, cyclophosphamide, deoxyspergualin, didemnin B, methotrexate, thalidomide, **rapamycin**, or combinations thereof.

. . . composition of claim 3, further comprising an effective amount of one or more immunosuppressants selected from the group consisting of: **tacrolimus**, mizoribine, azathioprine, cyclophosphamide, deoxyspergualin, didemnin B, methotrexate, thalidomide, **rapamycin**, or combinations thereof.

PI US 5540931 19960730

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SUMM Non-limiting examples of **penetration enhancers** which may be used as optional activity **enhancers** herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic. . . 2-hydroxypropanoic acid, 2-hyroxyoctanoic acid, methylsulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, **urea**, diethyl-m-toluamide,, 1-dodecylazacycloheptan-2-one and those described in U.S. Pat. No. 5,015,470, issued May 14, 1991 and U.S. Pat. No. 5,496,827, issued. . .

SUMM Other classes of optional activity enhancers for use herein include flavinoids, **ascomycin** derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those. . .

PI US 6124362 20000926

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L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **137071-32-0** REGISTRY
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 3-[(1E)-2-[(1R,3R,4S)-4-chloro-3-methoxycyclohexyl]-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 3-[2-(4-chloro-3-methoxycyclohexyl)-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-, [3S-[3R*[E(1S*,3S*,4R*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-
OTHER NAMES:
CN 33-epi-Chloro-33-desoxyascomycin
CN Elidel
CN Pimecrolimus
CN SDZ-ASM 981
FS STEREOSEARCH
MF C43 H68 Cl N O11
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as described by E or Z.